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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/800,622	03/16/2004	Chang-Yi Lin	LINC3186 CIP/EM	9676

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EXAMINER	
EBRAHIM, NABILA G	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
10/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/800,622	LIN ET AL.	
	Examiner	Art Unit	
	NABILA G. EBRAHIM	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,18-20 and 72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,18-20 and 72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of the appeal brief filed on 05/19/2009, PROSECUTION IS HEREBY REOPENED. New ground of rejection is set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final)or a reply under 37 CFR 1.113 (if this Office action is final); or, (2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

Status of claims:

Claims 1-16, 18-20 and 72 are pending in the application.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

1. Claims 1-11, 13-15, 18-20 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsuru et al. EP 376331 (Tsuru) in view of Lee et al WO 0015194 (Lee) and further in view of Isobe et al. US 5603945 (Isobe).

Tsuru teaches a slow release drug delivery granules comprising porous granules of a calcium phosphate compound having a ratio of Ca to P of 1.3 to 1.8, a porosity of 0.1 to 70%, a specific surface area of 0.1 to 50 m^2/g and a pore size of 1nm to 10 microns, fired at a temperature of 200 to 1400°C, and a drug component impregnated in pores of the granules, and a process for producing the same. The drug delivery granules of the invention has a controllable and good prolonged effect of the drug release and can be advantageously utilized in the field of a chemotherapy (abstract). The granule size can be of 5 to 500 microns, and most preferably a granule size of 10 to 100 microns (page 3, lines 46+); this disclosure reads on the sized recited on instant claims 1, 3 and 4. Tsuru discloses that the Ca/P ratio of 1.3 to 1.8. A ca/P ratio of 1.35 to 1.75 is preferable and a Ca/P ratio of 1.4 to 1.7 is more preferable (page 3, lines 15-16). Further, the porous granules have a specific surface area of 0.1 to 50 m^2/g, preferably 1 to 40 m^2/g, more preferably 10 to 30 m^2/g (page 3, lines 35+). A drug or medicine is contained in pores of the granules (page 2, line 51). The drugs contained in the pores include antibiotics (page 4, line 57). Example 6 teaches hydroxyapatite powder having a Ca/P ratio of 1.67 mixed with spherical acryl beads having an average size of 50 micron which serve as cores of granules in a stirrer and stirred under spraying of distilled water at a high speed of 5000rpm. The thus coated beads were fired at a temperature of 900 DEG C to obtain the hollow granules of hydroxyapatite

having an average granule size of 90 microns. These hollow granules have a porosity of 50%, average pore size of 200nm and specific surface area of 14.5m^2/g. The granules are impregnated in the ADR solution to obtain drug contained in the pores with the acryl polymer beads (example 6).

Regarding the amount of polymer and/or the amount of drug loaded, since Tsuru teaches that the drug and polymers are entrapped in the pores of the apatite and since the size of the pores are the same then the amount of entrapped substance in the pores is obviously the same and the amount of drug loading should be within the capabilities of a person of ordinary skill in the art.

Tsuru did not disclose binding of the granules into composite using a biocompatible polymer.

Lee teaches improved calcium phosphate delivery vehicle or adjuvant with incorporated adjuvanticity enhancing means. The adjuvant can be fabricated to desired formulations as appropriate and based on the intended purpose. Particle sizes can be adjusted to enhance adjuvant activity. Lee also teaches that an amorphous calcium phosphate adjuvant is disclosed. A poorly crystalline apatitic calcium phosphate adjuvant is disclosed. The reference teaches that apatitic calcium phosphorous ratios of 1.3-1.75, poorly crystalline forms are believed to resorb more quickly than highly crystalline forms (page 11, lines 19+) and that the porosity of the apatite proves the desirable characteristics for immunogen (active agent) delivery to form the inventive material (page 12, lines 1+). In a preferred embodiment, the calcium-based adjuvant is combined with poly-L-lactic acid (PLLA) and/or polyglycolide (PGA) for increased

flexibility. In addition, Lee teaches PLGA, PLA, gelatin), particularly biodegradable polymers, may also increase adjuvant activity by themselves serving as a delivery vehicle for the inventive calcium phosphate adjuvant (page 20, lines 25+). Further, Lee teaches in a preferred embodiment, a calcium phosphate adjuvant is prepared as a composite of calcium phosphates with different resorption rates. Variable delivery kinetics may be achieved by combining multiple calcium phosphates having different resorption rates within one adjuvant system (page 22, lines 9+). The reference discloses that the art knew that calcium phosphates were known as tablet disintegrators; suspending agents; flocculating agents; oral detoxifying antacids and others (page 2, lines 27+).

Thus, it would have been obvious to a person having ordinary skill in the art to use poly-L-lactic acid and/or polyglycolide (PGA) to the granules disclosed by Tsuru to add adjuvanticity and /or resorbability to an oral tablet made from the granules disclosed by Tsuru.

Both references did not teach the use of soluble polymers disclosed in instant claim 9 which are entrapped in the pores with the active agent.

Isobe teaches Therapeutic/prophylactic agents for pets. The reference teaches that the formulation includes ascorbic acid and discloses that in order to mask the taste and improve the palatability, the edible organic acid or a salt thereof, especially the powdery or granular edible organic acid or a salt thereof, may be coated, and the solid preparation may be a sugar coated solid preparation (e.g. tablet) or a coated solid preparation (e.g. tablet) coated with a coating base. The examples of the coating base

include gelatin, hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, low-substituted hydroxypropylcellulose, polyethylene glycol, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, acrylic acid copolymer, carboxymethylcellulose, carboxymethylethylcellulose, and polyvinyl alcohol

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to use the polymers disclosed by Isobe for taste masking such as cellulose polymers, polyethylene glycol and polyvinyl alcohol to mask the taste and/or improve palatability of drugs such as ascorbic acid. The person of ordinary skill would be motivated to include other drugs that are known to have a unacceptable taste with the said polymers in a taste masking preparation and include it in the granules taught by Tsuru because apatites are known to have a taste masking property which is evidenced by the following references: US 20030168401 which teaches porous hydroxyapatite used in water filters to reduce containants and improve taste, US 5648399 which teaches hydroxyapatites remove salty or metallic taste, and JP 62032872 which teaches alcoholic drink taste improving agent comprises granular or porous sinter of hydroxyapatite. Therefore, the soluble polymers having taste masking properties enhance the effect of hydroxyapatite and motivate a person having ordinary skill in the art to combine both the granules teaching and the polymers teaching since both are in the same field of endeavor.

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tsuru et al. EP 376331 (Tsuru) in view of Lee et al WO 0015194 and further in view of Makoto et al. "Effect of Sodium bicarbonate amount on in vitro indomethacin release from self-

setting carbonated apatite cement", Pharmaceutical Research, Vol. 14, No. 4, 1997 (hereinafter Makoto).

Tsuru and Lee are relied upon for the reasons set forth hereinabove.

Neither of the references teaches the amount of carbonate in the apatite.

Makoto studied adding sodium bicarbonate 0-10% to hydroxyapatite which resulted in increasing total pore volume of the cement matrix. Further, the reference teaches that mean drug release time and T_{50} (the time required for 50% drug release of the cement) were a function of adding the amount of sodium bicarbonate. The results of the relationship between the micropore distribution, total volume of pores after drug release and the drug release behavior supported the hypothesis that the variation in drug release from the cements resulting from the addition of sodium bicarbonate was mainly due to an increase in the diffusion of the drug in the micropores of the cement by dissolution or erosion of the cement matrix (see methods, results and conclusion).

Therefore, it would have been obvious to a person having ordinary skill in the art at the time the invention was made to use carbonated apatite having an amount of carbonate around 10% and optimize the amount of carbonate to control increasing or decreasing the pores in the apatite to the degree needed in the apatite and consequently to control the release of a drug from the granules disclosed by Tsuru using the polymers disclosed by Lee to obtained a controlled release drug that is entrapped in porous carbonated apatite.

Response to Arguments

Applicant's arguments with respect to claims 1-16, 18-20 and 72 have been considered but are moot in view of the new ground(s) of rejection.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NABILA G. EBRAHIM whose telephone number is (571)272-8151. The examiner can normally be reached on 9:00AM - 6:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NABILA G EBRAHIM/
Examiner, Art Unit 1618

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618